

The Neurotoxicity of Alcohol

The brain is a major target for the actions of alcohol, and heavy alcohol consumption has long been associated with brain damage. Studies clearly indicate that alcohol is neurotoxic, with direct effects on nerve cells. Chronic alcohol abusers are at additional risk for brain injury from related causes, such as poor nutrition, liver disease, and head trauma.

The potential cost to society of alcohol-induced brain damage is enormous. Approximately 14 million Americans—about 7.4 percent of the adult population—meet the diagnostic criteria for alcohol abuse or alcoholism (Grant et al. 1994). On any given day, more than 700,000 people in the United States receive alcoholism treatment in either inpatient or outpatient settings (National Institute on Alcohol Abuse and Alcoholism [NIAAA] 1997). Approximately 9 percent of alcohol-dependent individuals have clinically diagnosable brain disorders (Eckardt and Martin 1986). Indeed, alcoholic dementia is the second-leading cause of adult dementia in the United States, accounting for 10 percent of cases (Eckardt and Martin 1986). It is exceeded only by Alzheimer's disease. Many studies report that 50 to 75 percent of detoxified long-term alcohol-dependent individuals show some degree of cognitive impairment (Eckardt and Martin 1986), suggesting that brain dysfunction may persist even after the individual has stopped drinking.

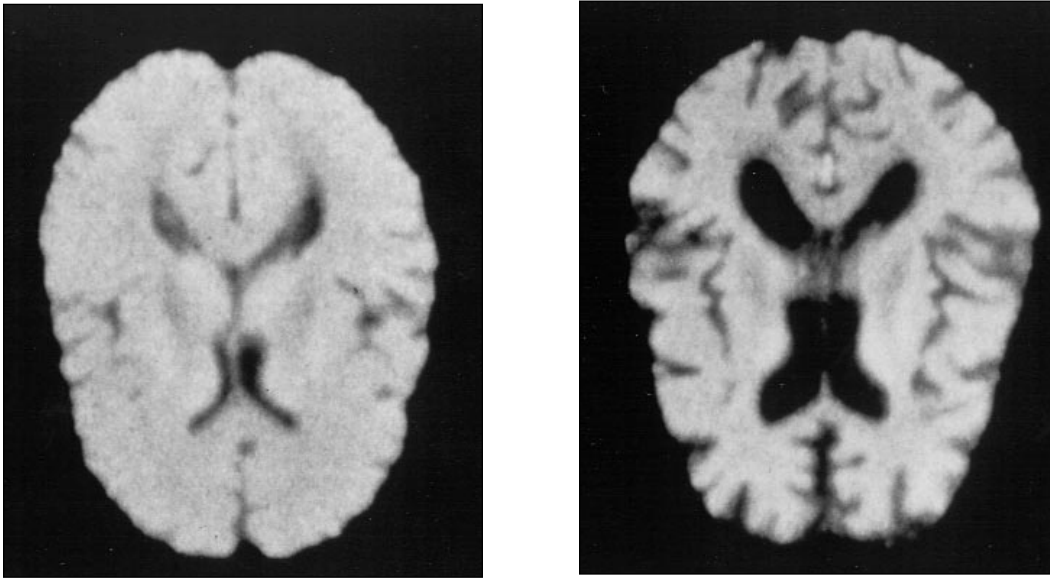
Individual susceptibility to alcohol-induced brain damage is highly variable and is related to many factors, such as gender, genetics, environment, and sociodemographics (Dufour 1993). Susceptibility to alcohol dependence is similarly variable; some people become dependent at much lower levels of consumption than others do. Therefore, it is difficult to specify the levels of alcohol consumption that are likely to lead to alcohol-induced brain damage. There is a serious need for further research in this area.

Neuropathologic Changes

The brain contains as many as 1 trillion nerve cells, or neurons. They come in a variety of shapes and sizes, some looking like old oak trees and others like weather balloons. Many of these cells project into other brain areas where they regulate the activity of those areas, thereby affecting thoughts, consciousness, decisions, mood, and attention. For every nerve cell in the brain that is actively engaged in such things as thoughts, emotions, and movements, there are 10 other cells, called glia, that provide important support to nerve cells. Both of these cell types are damaged by chronic alcohol abuse. Loss of a critical few due to alcohol-induced brain damage may have subtle but important effects on decision-making processes, mood, and behavior.

There appears to be a continuum of brain damage in long-term alcoholics, progressing from moderate deficits in the majority of long-term alcohol abusers to the severe psychosis of Wernicke-Korsakoff syndrome (Butterworth 1995; Pfefferbaum et al. 1996). This syndrome includes Wernicke's encephalopathy and Korsakoff's psychosis, also called Korsakoff's amnesic syndrome. Wernicke's encephalopathy is associated with thiamine deficiency resulting from malnutrition. Prompt treatment with massive doses of thiamine may improve symptoms of this disorder, which include confusion, ataxia (disordered gait), and visual abnormalities. Patients have characteristic brain lesions that may be detected by magnetic resonance imaging (MRI). Korsakoff's psychosis is characterized by anterograde amnesia, where the individual is unable to retain new information (Eckardt et al. 1981). For example, the patient views as total strangers people who were encountered moments before. The memory dysfunction correlates with the presence of lesions in the thalamus, a brain structure involved in the routing of sensory information in the brain.

Figure 1: Reduced brain mass in alcoholics



Axial magnetic resonance images from a healthy 57-year-old man (left) and a 57-year-old man with a history of heavy alcohol consumption (right). Images are courtesy of Dr. Adolf Pfefferbaum.

(Victor et al. 1989). Although these two conditions usually occur in sequence, they may exist independently; not all patients with Wernicke's encephalopathy progress to Korsakoff's psychosis, and Korsakoff's psychosis may occur without a preceding episode of Wernicke's encephalopathy.

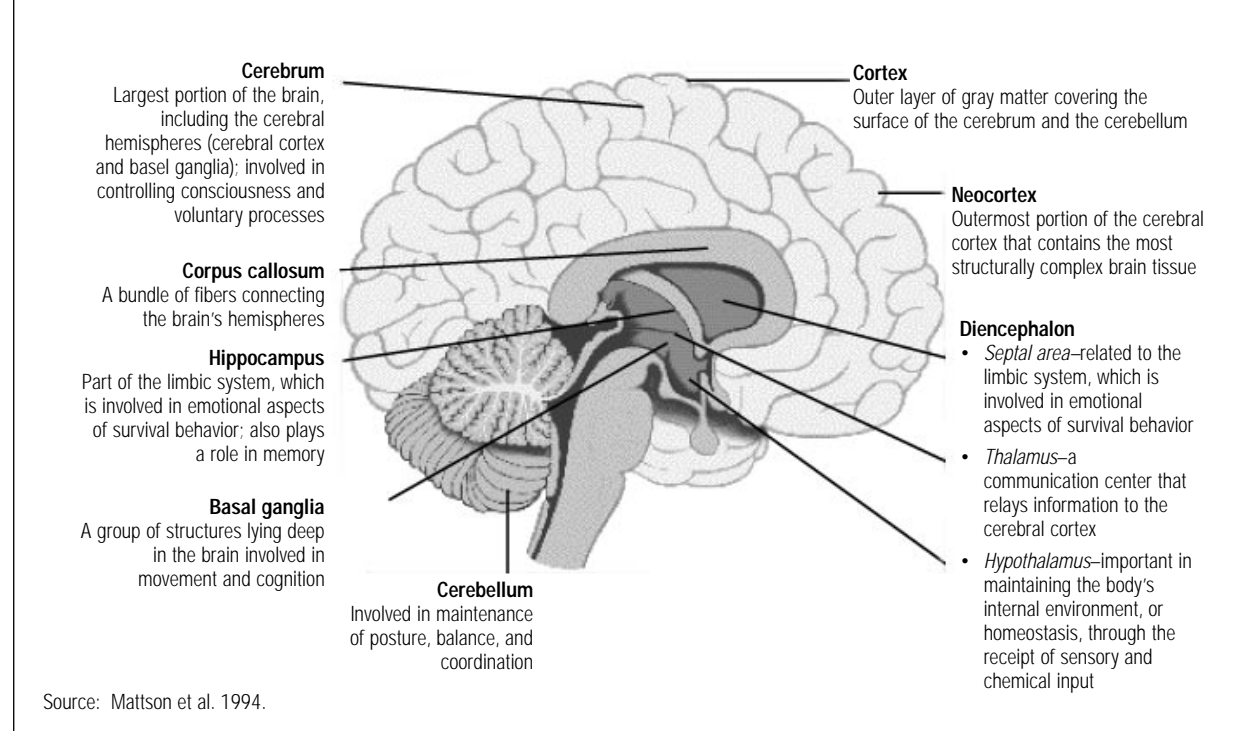
Extremely heavy alcohol consumption for a prolonged period is generally required to produce the most severe organic brain disease. One study that compared Wernicke-Korsakoff patients with alcoholics who did not have serious neuropsychological deficits found that both age of onset and duration of heavy drinking correlated with the development of Korsakoff's psychosis (Jacobson 1990). Those with Wernicke-Korsakoff syndrome began consuming approximately 12 drinks a day at age 25 and drank at that level for 27 years.

Morphological Changes

Postmortem studies of brain tissue in both humans and animals suggest that chronic heavy alcohol use changes brain structure. These

observations are supported by imaging analyses. For example, studies using MRI and computed tomography (CT) show enlargement of the cerebral ventricles (cavities within the brain that are filled with cerebrospinal fluid) and sulci (furrows on the surface of the cerebrum) in most alcoholics. Enlargement of these structures reflects a shrinkage of brain mass (figure 1), consistent with postmortem studies that show reduced brain weight in alcoholics. In severe alcoholics, the reductions in weight of the cerebral hemispheres and the cerebellum (a brain structure predominantly involved in balance and movement; see figure 2) are significant compared with nondrinkers and moderate drinkers (Harper and Kril 1993). The reduced brain mass is probably due to a combination of actual loss of nerve cells and reduction in cell size. With sustained abstinence for 1 to 5 months, the defect begins to disappear. This recovery probably involves increases in neuronal cell size, number and size of the supporting glial cells, and arborization (branching) of nerve endings (Franke et al. 1997). However, neurons that die are lost forever.

Figure 2: Anatomy of the brain



Data from tissue and quantitative morphometry (structural) studies demonstrate selective neuronal loss, reduced arborization, and reduction of synaptic complexity in specific brain regions of alcoholics. The frontal lobes (of the cerebrum)—whose functions encompass the initiation of motor activity and the integration of behavior, intellect, and emotion—appear to be particularly sensitive to alcohol-induced changes (Jernigan et al. 1991). They show the greatest decrease in mass and account for much of the associated ventricular enlargement. Both gray matter, which is composed largely of neurons, and white matter, which is composed of myelinated nerve fibers, appear to be decreased. (The myelin sheath around nerve fibers facilitates the conduction of nerve impulses.) There appears to be a selective loss of white matter, particularly in the frontal lobes, but it is uncertain how the observed cellular lesions relate to this loss. One reason these changes are more evident is the greater proportion of white matter to cortical gray matter in the frontal regions. (Cortical refers to the cerebral cortex, a thin layer of gray matter on the surface of the cerebrum. It is most extensively

developed in humans; among its functions, it is the center for intellectual capacity.) Alcoholics with severe brain disorders, such as Wernicke-Korsakoff syndrome, show more significant reduction in white matter and more extensive brain degeneration than do alcoholics with less severe disorders.

Investigators have found a 22-percent reduction in the number of neurons in the superior frontal cortex and motor cortex of alcoholics compared with nonalcoholic controls, but no significant differences in other areas of the cortex (Harper et al. 1987). Recent studies of alcoholics have reported a relationship between temporal lobe shrinkage and a history of alcohol withdrawal seizures, while frontal lobe shrinkage occurs in alcoholics regardless of their seizure history (Sullivan et al. 1996). A decrease in the amount of *N*-acetylaspartate in the frontal lobe, a measure of neuron viability, is another indication of frontal lobe degeneration in alcoholics (Jagannathan et al. 1996). The findings of severe damage to the frontal cortex in alcoholics are consistent with clinical and neuroradiological findings, which

suggest that the frontal lobe may be more susceptible than other cortical regions to alcohol-induced brain damage. The large neurons that are lost in this frontal region (the pyramidal neurons) are also recognized as being more vulnerable in Alzheimer's disease and as part of the normal aging process.

Recent studies have found that in addition to the global shrinkage of brain regions, neurons in certain structures called nuclei are selectively lost with chronic alcohol abuse. Nuclei are clusters of neurons that have broad-ranging functions in brain activity; they are distinguishable by cell type or by clear demarcation from the surrounding tissue. Perhaps the most extensively studied nuclei are the cholinergic nuclei in the basal forebrain. Neurons within these nuclei are involved with the production and release of acetylcholine, a neurotransmitter associated with many important physiologic functions. Both human and animal studies suggest that this region is particularly susceptible to damage in alcoholic subjects. Researchers have reported that Korsakoff's psychosis causes both neuronal loss and shrinkage in this area, with one study reporting a significant loss of neurons (Arendt 1993). Neurons in the cholinergic nuclei are also lost in Alzheimer's disease.

Other brain nuclei that appear to be particularly sensitive are the locus ceruleus and the raphe nuclei. These nuclei are small but important because their neuronal processes project throughout the brain and modulate global aspects of brain activity. For example, lesions in the locus ceruleus, which contains many of the noradrenergic neurons (those that secrete the neurotransmitter norepinephrine) in the brain, may impair attention and information processing and may affect learning and memory. Several studies have reported significant noradrenergic cell loss in the locus ceruleus (Arango et al. 1996; Arendt et al. 1995; Lu et al. 1997), but not all studies have found this loss (Harper and Kril 1993). The median and dorsal raphe nuclei together provide the primary source of serotonergic axons in the cerebral cortex. These neurons secrete serotonin, a neurotransmitter that affects multiple actions in

the brain, including the regulation of mood states, thinking patterns, appetite, sleep, and even behavior, such as alcohol drinking. The serotonergic system appears to be disrupted in alcoholics, particularly in severe alcoholics (Baker et al. 1996; Halliday et al. 1995). Recent studies of alcoholics have found a reduction of up to 50 percent in the number of serotonergic neurons from both these raphe nuclei compared with nonalcoholic controls. Further, chemical studies have shown abnormally low levels of serotonergic metabolites in the cerebrospinal fluid of alcoholics with Wernicke-Korsakoff syndrome.

Specific types of brain cells appear to be disrupted. Recent studies have indicated that certain neurons containing the peptide vasopressin may be sensitive to chronic alcohol-induced neurotoxicity in both humans and animals (Harding et al. 1996; Madeira et al. 1997). Vasopressin is a hormone that is involved in the regulation of both physiologic processes and neurobehavioral function. Damage to neurons containing vasopressin and other peptides could disrupt a variety of hormone functions as well as the daily rhythms that are important for healthy living. Further studies are needed to determine whether additional specific cell groups within the brain are particularly susceptible to damage. Neuronal loss in small but functionally significant brain areas could result in global changes in attention, mood, and personality that are difficult to quantify but have a great impact on brain function and overall behavior.

Recent animal studies have found that long-term alcohol intoxication is not necessary for brain damage to occur. As little as a few days of intoxication can lead to neuronal loss in several specific areas of the cerebral cortex (Collins et al. 1996). These findings are consistent with recent studies in human alcoholics that report damage to one of these cortical areas (Ibanez et al. 1995) and significant shrinkage of the hippocampus, an area involved in learning and memory (Harding et al. 1997). Chronic alcohol treatment of animals has shown that hippocampal damage is correlated with deficits in spatial learning and memory (Franke et al. 1997). These studies indicate that

cortical and hippocampal damage can occur in animals with both chronic and short-term alcohol exposure. This suggests that, in humans, relatively short durations of alcohol abuse are likely to cause some form of damage.

Exciting new studies have begun to address the effects of gender on alcohol-induced brain damage. Interestingly, alcoholic women appear to have an increased sensitivity for brain damage compared with alcoholic men (Hommer et al. 1996). This difference appears to be true for liver and heart damage as well. Although more men than women are diagnosed as alcoholic, the number of alcoholic women is increasing. Therefore, the increased susceptibility of women to alcoholic brain damage is an area that needs further investigation.

Functional Changes

Chronic alcohol abuse clearly leads to changes in brain function, with the degree of dysfunction dependent upon the duration and amount of alcohol consumed. Many brain functions related to the frontal cortex appear to be affected. Prefrontal (the most anterior part of the cortex) damage typically is associated with changes in personality and cognitive abnormalities. Although these types of changes in brain function are more difficult to assess than physical changes, they are consistent with the morphological changes found in the frontal cortex of alcoholics.

Both clinical and experimental studies support a role for frontal cortical involvement in neuropsychological deficits in alcoholics, particularly those with Korsakoff's psychosis (Oscar-Berman and Hutner 1993). These deficits include dysfunction in emotional control, problem-solving ability, and attention. Electrophysiologic studies using electroencephalograms and event-related potentials have suggested that alcoholics have difficulty differentiating relevant and irrelevant, easy and difficult, and familiar and unfamiliar stimuli (Porjesz and Begleiter 1993). These deficits appear to be consistent for alcoholics and may be related to frontal cortical function.

Alcoholics who do not suffer from Wernicke-Korsakoff syndrome still show greater loss of neuropsychological performance than peer nonalcoholics do on tests of learning, memory, abstracting, problem solving, visuospatial and perceptual motor functioning, and information processing (Parsons 1993). Alcoholics are less accurate and take considerably longer to complete tasks. Many of the deficits appear to recover to age-appropriate levels of performance after 4 to 5 years of abstinence (Parsons 1993). However, even though global cerebral atrophy may return to near normal levels with extended abstinence, not all cognitive functions return. Some abstinent alcoholics appear to have permanent cognitive impairments, particularly in memory and visual-spatial-motor skills (Di Sclafani et al. 1995). Other studies support a loss of logical memory and paired-association learning tasks in alcoholics that may be long lasting (Eckardt et al. 1996).

Recent studies have emphasized the role of the prefrontal cortex in executive cognitive function (ECF) (Hoaken et al. 1998). This is the ability to use higher mental processes such as attention, planning, organization, sequencing, abstract reasoning, and the use of external and internal feedback to adaptively shape future behavior (Foster et al. 1994). ECF processes are dysfunctional in alcoholics and in persons with other diseases showing prefrontal damage (Boller et al. 1995). Changes in ECF and prefrontal cortical characteristics are associated with decreased regulation of human social behavior, including disinhibition syndrome, which is characterized by impulsivity, socially inappropriate behavior, and aggression (Giancola and Zeichner 1995*a*). Disruption of ECF has also been implicated in the underlying aggression associated with substance abuse (Giancola and Zeichner 1995*b*).

Mechanisms of Action

Researchers have only recently begun to elucidate the mechanisms involved in the neurotoxic effects of alcohol on the brain. As research techniques have become more sophisticated and data from experimental and clinical studies have accumulated, however, investigators have had a more

substantial basis for speculation as to the nature of these mechanisms.

NMDA Receptor Supersensitivity

One promising avenue of research involves the interaction between glutamate, an amino acid that is the major excitatory neurotransmitter in the brain, and a specific glutamate receptor, the *N*-methyl-D-aspartate (NMDA) receptor. Glutamate and the NMDA receptors are extensively discussed in other sections of this chapter. The NMDA receptor is inhibited by alcohol at a greater level of sensitivity than is any other known glutamate receptor. The acute alcohol-induced inhibition leads to adaptive changes in the NMDA receptor that make it supersensitive to glutamate during chronic alcohol exposure.

Excessive stimulation of NMDA receptors by glutamate can kill neurons, and chronic alcohol exposure increases sensitivity of neurons to NMDA-stimulated killing (Chandler et al. 1993*a*; Crews and Chandler 1993; Iorio et al. 1993). Excitotoxicity is a term applied to the direct lethal damage to neurons in extreme cases of excessive glutamate receptor activity, usually accompanied by an excessive accumulation of intracellular calcium ions. This neurotoxic property of the receptors appears to play a key role in neurodegenerative diseases in general, as well as in stroke, brain trauma, and other types of brain damage (Crews et al. 1996). The extreme neurodegeneration associated with Wernicke's encephalopathy also appears to involve increases in glutamate-NMDA excitotoxicity. Several studies using cultured neuronal cells have indicated that a few days of chronic alcohol treatment lead to supersensitive NMDA receptor-stimulated calcium flux (an increase in the intracellular concentration of calcium ions) (Ahern et al. 1994; Iorio et al. 1992), as well as NMDA receptor-stimulated excitotoxicity (Chandler et al. 1993*b*; Crews and Chandler 1993; Crews et al. 1993; Iorio et al. 1993) and NMDA receptor-stimulated nitric oxide formation (Chandler et al. 1997). All of these reactions lead to severe neuronal damage.

The administration of an antagonist to NMDA receptors, such as MK-801 (dizocilpine), eliminates both alcohol tolerance (Khanna et al. 1992; Szabo et al. 1994) and withdrawal seizures (Grant et al. 1990), as well as blocks NMDA-stimulated neuronal death (Chandler et al. 1993*a*). In animal studies using thiamine-deficient rats as a model for Wernicke's encephalopathy, extracellular concentrations of glutamate in the brain increased several fold during seizures (Langlais and Zhang 1993). Administration of the NMDA receptor antagonist MK-801 reduced the neurobiological symptoms and the severity of neural lesioning in these animals (Langlais and Mair 1990). These studies and others provide evidence that NMDA receptor supersensitivity may contribute to alcohol tolerance, dependence, and neurotoxicity and to the hyperexcitability and seizures associated with alcohol withdrawal. However, further research is needed in this area.

Hyperexcitability of the central nervous system is a key component of alcohol withdrawal. A supersensitive glutamate-NMDA response appears to be involved, although a reduction in gamma-aminobutyric acid-mediated inhibition also may contribute to this hyperexcitability (Crews et al. 1996). (Gamma-aminobutyric acid is a neurotransmitter that inhibits the activity of nerve cells.) One of the earliest findings suggesting glutamate involvement was the increased binding of radioactively labeled glutamate ($[^3\text{H}]\text{glutamate}$) in the hippocampus of alcoholics (Michaelis et al. 1990). Although it is not clear which subtype of glutamate receptor is involved, this finding is consistent with increased glutamate receptor density and sensitivity.

The mechanisms of NMDA receptor supersensitivity are not fully understood, but it is clear that chronic alcohol administration can induce this supersensitivity. This supersensitivity could occur through a number of mechanisms, including an increase in the density of NMDA receptors, changes in the NMDA receptor subunit composition, or chemical changes in the NMDA receptor that could change its sensitivity. Some, but not all, studies have found increases in NMDA receptor density. These results, although

inconclusive, suggest that this may be one of the mechanisms underlying chronic alcohol-induced NMDA receptor supersensitivity (Chandler et al. 1997; Crews et al. 1996; Rudolph et al. 1997).

A second mechanism for inducing NMDA receptor supersensitivity could involve changes in the subunit composition of the receptor. The NMDA receptor is thought to be made up of five subunits, and changes in the type of subunit could change NMDA receptor supersensitivity. Studies have reported that the number of subunits expressed during chronic alcohol exposure is altered (Follesa and Ticku 1995, 1996).

Other studies, however, found alcohol-induced NMDA receptor supersensitivity without subunit changes (Chandler et al. 1997), suggesting that other mechanisms, such as phosphorylation, might be involved. This is a chemical reaction that is involved in regulation of receptor activity. Enzymes that phosphorylate (add phosphate to) amino acid residues within the NMDA receptor, including tyrosine kinases such as Fyn tyrosine kinase, may affect NMDA receptor sensitivity during alcohol treatment (Miyakawa et al. 1997). These mechanisms could occur as a continuum, with phosphorylation causing initial supersensitivity, and more prolonged and excessive alcohol consumption causing additional supersensitivity through changes in subunits and slight increases in NMDA receptor density. Because of the consistent finding that NMDA supersensitivity during chronic alcohol treatment leads to increased NMDA receptor-stimulated neuronal excitotoxicity, all of these mechanisms are being further investigated.

Oxidative Stress

Another possible mechanism for alcohol-induced brain damage involves oxidative stress of neurons. As a by-product of alcohol metabolism, free radicals may be formed. These are highly reactive molecular fragments that are capable of inflicting serious damage on cells if they are not quickly neutralized. Normally, free radicals are rapidly inactivated by antioxidants, which are protective molecules that inhibit oxidation. However, if these defenses are impaired, or if there is an

overproduction of free radicals, the result is oxidative stress. This imbalance between increased production of free radicals and decreased availability of antioxidants can result in cell death. Free radicals also may attack lipids in cell membranes, causing lipid peroxidation. This is a reaction between oxygen radicals and components of the cell membrane that results in membrane injury and eventual cell death.

Studies examining the effects of both acute and chronic alcohol administration on cellular oxidation in the rat brain have focused primarily on alcohol's effects on the activity of antioxidants, such as alpha-tocopherol, ascorbate, glutathione, catalase, and superoxide dismutase (Ledig et al. 1981; Montoliu et al. 1994; Nordmann 1987; Rouach et al. 1987), or on potential sources of oxidative radicals. One of these sources is nitric oxide, which has been implicated in neuronal toxicity resulting from the formation of highly oxidative metabolites (Crews and Chandler 1993). Another source of oxidative radicals is cytochrome P450 2E1, an enzyme that metabolizes alcohol and is a potent generator of these radicals (Montoliu et al. 1994, 1995). Increases in cytochrome P450 2E1 and other oxidases induced in rats by chronic alcohol administration have been related to increased lipid peroxidation and the formation of reactive oxygen radicals in the brain (Montoliu et al. 1994). However, levels of antioxidant enzymes, such as catalase and superoxide dismutase, appear to increase as a compensatory mechanism (Montoliu et al. 1994).

The brain is particularly susceptible to lipid peroxidation because it consumes a large amount of oxygen and is rich in polyunsaturated fatty acids, which are particularly prone to injury from oxygen radicals. Experiments with cells of rat brains have shown that a single dose of alcohol results in both increases in lipid hydroperoxide levels and decreases in glutathione levels (Nordmann et al. 1990, 1992; Uysal et al. 1986, 1989). It is not clear whether or how this increased oxidation is associated with increased brain damage. Most studies have focused on whole-brain homogenates, rather than on cells of specific brain regions. However, a recent study of

alcohol-induced depression of glutathione and glutamine synthetase levels, two indices of increased oxidative radical formation, used cells from specific brain regions. Researchers found changes only in cells from the striatum (a center involved in the programming of movement), but not in cells from the cerebral cortex or cerebellum (structures involved in balance and motor coordination) (Bondy and Guo 1995).

Oxidative stress has been implicated in the effects of aging and in a variety of neurodegenerative disorders, such as Alzheimer's disease, Parkinsonism, and stroke. Much more research on alcohol-induced neurodegeneration is needed to provide a more complete understanding of how oxidation damages neurons and how other brain cells respond to increased oxidative stress. Alcohol-induced neurodegeneration may be related to an induction of oxidative enzymes; alcohol research provides an opportunity to clearly address this aspect of neurodegeneration, which could impact a broad range of diseases.

Growth Factors

Growth factors are specific protein elements of the brain that stimulate growth and extensions of neurons and that are essential to neurons for their survival and maintenance of normal function. Growth factors also are known to increase the activity of neuronal antioxidant and excitotoxic protective mechanisms. The growth factors include, among others, nerve growth factor (NGF), brain-derived neurotrophic factor (bDNF), neurotrophin 3 (NT-3), and basic fibroblast growth factor (bFGF).

Researchers have found that alcohol alters brain levels of growth factors in rats (Arendt et al. 1995; Baek et al. 1996; MacLennan et al. 1995; Nakano et al. 1996). Recent studies have found that chronic alcohol administration reduces the level of bDNF but does not change the levels of NGF, NT-3, or bFGF (Baek et al. 1996; MacLennan et al. 1995). Receptors for the growth factors remain intact after chronic alcohol abuse (Arendt et al. 1995; MacLennan et al. 1995). This finding presents the promising

possibility that growth factors may be used to treat alcohol-induced brain damage as well as other neurodegenerative conditions. Studies of the actions of growth factors and of their role in alcohol-induced brain damage represent an exciting new area of discovery that could provide new approaches to treatment of neurodegeneration.

In Closing

Alcoholism is a progressive disease that starts with experimentation and progresses to addiction, usually over the course of several years. Addiction involves the loss of control over the ability to abstain from the drug and an excessive preoccupation with obtaining and using the drug. Discoveries continue to unravel structure-function aspects of the brain and suggest that some of the behavioral problems of alcoholism may be related to alcohol-induced damage to specific brain areas. While earlier studies focused on alcohol-induced changes in cognition, more recent studies are focusing on the frontal cortex, which is particularly sensitive to alcohol-induced damage, and on the role of this brain region in behavior. Experimental subjects with poor prefrontal functioning appear unable to inhibit impulsive behavior (Lau and Pihl 1996), particularly violence (Lau et al. 1995). Results of neuroimaging studies also indicate that reduction of metabolic functions in the frontal lobes is associated with violence (Raine et al. 1994).

Taken together, these studies suggest that some of the greatest sociopathic problems of alcoholism, such as violence and loss of control over the drug, may be directly related to the neurotoxic effects of alcohol on prefrontal cortical function. This is a particularly exciting hypothesis, because it suggests that it may be possible to detect individuals at risk for addiction through studies of their brain function and to determine whether recovery of normal function is associated with the ability to sustain abstinence. Identification of these individuals would allow focused efforts at prevention and education, with the aim of preventing addiction and its accompanying sociopathic behaviors.

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